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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

December 17, 1993

In re Application of:		Byoung Se Kwon
Serial No.:		07/012,269
Filed:		2/1/1993
For:		NEW RECEPTOR, MONOCLONAL ANTIBODY, LIGAND PROTEIN AND METHODS FOR USE
Examiner:		J. Ellis
Art Unit:		1813

RESPONSE TO OFFICE ACTION

In response to the office action dated September 17, 1993, please amend the claims and consider the following remarks.

In the Specification

Page 5, line 28, please add the word --to-- before the word "enhance".

Page 5, line 30, please replace the word "anti-immne" with the word --anti-immune--.

Page 6, line 7, please replace the word "know" with the word --known--.

Page 53, line 27, please replace the word "billidillg" with the word --binding--.

Page 55, line 8, please replace the word "miniml" with the word --minimal--.

Page 55, line 22, please replace the word "receptro" with the word --receptor--.

Page 55, line 28, please replace the word "mimicklng" with the word --mimicking--.

Page 56, line 12, please replace the word "inonoclonal" with the word --monoclonal--.

Page 56, line 16, please replace the word "hunan" with the word --human--.

Page 57, line 9, please replace the word "regullate" with the word --regulate--.

Group IV: Claims 21, drawn to a method of inducing B cell proliferation.

The restriction requirement as made is respectfully traversed. The Examiner has made no assertion nor demonstrated any serious burden to support the restriction requirement. MPEP §803 states:

> "There are two criteria for a proper requirement for restriction between patentably distinct inventions:
>
> (1) The inventions must be independent or distinct as claimed; and
>
> (2) There must be a serious burden on the examiner if restriction is not required.
>
> Where plural inventions are capable of being viewed as related in tow ways, both applicable criteria for distinctness must be demonstrated to support a restriction requirement."

The Examiner admits that the inventions are related but has failed to allege any burden other than to state that the inventions could be classified separately. However, the Examiner provides no explanation regarding how the separate classification creates any burden whatsoever. Any thorough search for a cDNA sequence would also include a search for homologous amino acid sequences and vice versa. Likewise keyword searching in electronic databases will result in discovery of relevant art for cDNA sequences, proteins, monoclonal antibodies and methods of use of the claimed inventions. A search for the term "4-1BB" or for portions of the cDNA or amino acid sequence will turn up relevant art for each of the inventions. The restriction requirement is believed to be improper because the Examiner has failed to make a prima facie case to support the requirement.

In order to be fully responsive the applicant must confirm the initial election of a group of claims. The applicant confirms the election of Group I for further prosecution. Specifically, claims 1-5 are elected for further prosecution.

The Rejection Under 35 U.S.C. §101

Claims 1-5 were rejected under 35 U.S.C. §101 as lacking patentable utility. This rejection is respectfully traversed.

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The Examiner states that "the specification fails to teach the biological activity of the protein encoded by Figure 2A. The Examiner also states:

> "In view of all the data, the specification proposes several roles for the 4-1BB protein such as a known or unknown neurotrophic factor (p. 43, lines 8-9), an accessory signaling molecule during T cell activation (p. 43, line 26), a cell surface receptor for T cells (p. 55, lines 12-14), etc.; however, the actual function of 4-1BB is not clear. Note that Chalupney et al. Proc. Natl. Acad. Sci. USA 89:10360 (1992) also teach that the function of 4-1BB is not known and the role of the 4-1BB gene product is difficult to predict. See p. 420, line 23. Furthermore, assuming arguendo that 4-1BB is a receptor protein, the specification fails to disclose the utility of a cDNA sequence which encodes an unknown receptor for an unknown ligand."

The Examiner's statements are incorrect. The specification provides detailed analysis of the expression and function of the 4-1BB gene and protein. 4-1BB is an inducible receptor-like protein expressed in both cytolytic and helper t-cells, PMA-treated spleen cells, heart cells, kidney cells and the brain. Crosslinking of 4-1BB on anti-CD3-stimulated T cells with the monoclonal antibody, 53A2, resulted in a dramatic enhancement of T cell proliferation. Furthermore, the addition of paraformaldehyde-fixed SF21 cells expressing recombinant 4-1BB, synergized with f(ab'), anti-μ in inducing splenic B-cell proliferation. The cDNA sequence is used to produce the recombinant protein that was later used to develop the monoclonal antibody.

Like any good scientist, the applicant realizes that there is a lot more to learn about 4-1BB, however, this does not mean that there is not a great deal known already. Frankly, there is no invention that could not use further analysis. The entire concept of invention is based upon further discovery and improvement. The specification includes many references to potential new areas of study and further research possibilities but this does not mean that nothing is known about 4-1BB or its function. The effects of 4-1BB have been discovered, specifically, T-cell proliferation and activation and B-cell proliferation. Doctors know that ibuprofin cures a headache but they knew relatively little about how it cures the headache. The applicant has clearly demonstrated how 4-1BB, the monoclonal antibody can be used in a utilitarian way.

The limitations of 35 U.S.C. §101 as interpreted in Brenner v Manson 383 U.S. 519, 148 U.S.P.Q. 689 (1966) requires that the utility must be a practical utility, however, this

practical utility does not have to rise to the level of a commercial utility. Brenner v Manson related to a process for making a steroid with no known function. the applicant does not rely on a "class of compounds" theory, but as an aside, it is the opinion that any sequence that encodes a protein that is a signaling molecule is inherently useful whether the function is known or not. However, 4-1BB has a known function that is useful that has been clearly demonstrated in the specification. The present specifications satisfies the requirement of 35 U.S.C. §101 by teaching the uses for the 4-1BB cDNA, protein and monoclonal antibody. Therefore, the reconsideration and withdrawal of this rejection is requested.

The Rejections and Objection Under 35 U.S.C. §112

The specification has been objected to under 35 U.S.C. 112, first paragraph as failing to provide an adequate written description. Claims 4 and 5 were rejected under 35 U.S.C §112, first paragraph. Claims 1-5 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claims the subject matter which applicant regards as his invention.

With respect to claim 5, the claim has been cancelled in favor of the CIP patent application referred to above which includes similar claims.

With respect to claim 4, the Examiner objects to the use of the phrase "fragments and derivatives" as used in claim 4 arguing that the specification does not teach what "fragments" or "derivatives" are intended. This is not true. The applicant discloses that the probes must be capable of being used to isolate similar sequences. This is a functional limitation, not a mere recitation of an intended use. The term "similar" is not vague or indefinite because, a DNA probe can not by used to determine anything other than homology. DNA probes are not used in activity assays (activity assays would show functional similarity) for lymphokines. References discussing the intercrine ß subfamily have been incorporated by reference into the specification. The conserved sequence fragments would make the most likely candidates for probes. This is well known and inherent from the information provided to anyone skilled in the art. Furthermore, many modifications can be made to the cDNA sequence without affecting the encoded amino acid in any way. Therefore, many derivatives are easily contemplated without any affect on the coded protein. These substitutions can be discovered merely by looking on a table listing the codons for each amino acid in any biochemistry book.

For reasons set forth above, the rejection of claim 4 under 35 U.S.C. § 112, first and second paragraph, is believed to be in error. The Examiner's reconsideration and withdrawal of the rejection is requested.

With respect to claims 1-3, the Examiner's suggestions have been incorporated into the amendments made above. In view of these amendments, the rejection of claims 1-3 under 35 U.S.C. § 112, second paragraph, is no longer believed to be proper. The Examiner's consideration of the amended claims and withdrawal of the rejection is requested.

The Rejection Under 35 U.S.C. §103

Claims 1-5 were rejected under 35 U.S.C. §103 as being unpatentable over Kwon in view of Maniatis et al.

Kwon et al only identified several cDNA clones which were partial fragments of the genes claimed herein. Nothing in Kwon et al taught which subset clones corresponded to the full length clone disclosed herein. Although that paper disclosed part of the method used to make this invention, it did not teach the complete structure of the cDNA sequence of the present invention. Although, it may be argued that the results of the prior paper might have made it obvious to try to determine the genes from which the fragments might have come, there was no indication in that work that the genes would be found, nor that those genes in their complete form would have the properties of 4-1BB as disclosed in the specification. In fact many of the subset clones were fragments of the previously known gene sequences. Although Maniatis et al does teach relevant techniques used in molecular biology, nothing in that reference would give a researcher skilled in the art reasonable expectation of success that those subset clones could be used to isolate the 4-1BB cDNA sequence having the properties disclosed in the specification. It was unknown whether these subset cDNA clones corresponded to novel proteins until the work disclosed in the specification.

Kwon et al does not put the actual subset clones into the hands of the public. Only the present inventor had the actual clone. Merely stating that a subset clone exists is insufficient to enable one skilled in the art to obtain it. This is the reason for the deposit rules with regard to biotechnology inventions. Synthesizing the sequence was not possible because no sequence was given. Following the same procedure would not necessarily produce the same subset clones and without access to the original subset clones it would be impossible to know whether the same clones had been made or not.

The Examiner has failed to recognize the importance of the teachings of the present invention that specifically identify the expression of the cDNA sequence. The sequence data disclosed in the present application was also important in determining which of the 14 initial cDNA isolates corresponding to the five species identified. Therefore, the two novel species L2G25B and 4-1BB were not positively identified until the sequence data was performed. While sequencing may have been obvious to try, the results of the sequence data were not obvious.

The applicant and the applicant's agent believe that all of the pending claims are in condition for allowance. Therefore the favorable reconsideration and early allowance of claims 1-4 and 6-21 is earnestly solicited.

Respectfully submitted,
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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this correspondence is being facsimile transmitted to the Commissioner of Patents and Trademarks, Washington, D.C. 20231 on December 17,1993.

Christopher A. Michaels